

Suzuki-Miyaura coupling under microwave enhanced conditions: synthesis of 2-(hetero)aryl benzimidazoles

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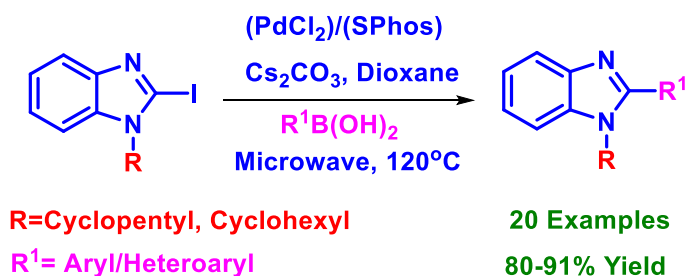
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Abstract

An expedient, palladium-mediated cross-coupling approach to functionalize the benzimidazole-based core under microwave-assisted conditions has been developed and is described. This protocol, which incorporates appendage diversity on this potential scaffold, is found to be compatible with a wide range of electronically- and sterically-divergent (hetero)aryl boronic acids. The use of the PdCl₂/(SPhos) catalytic system allows the formation of a stable and highly active LPd(0) species which was found to be critical for the successful synthesis of these novel, pharmacologically-relevant molecules.



Keywords. Benzimidazole, microwave, PdCl₂, SPhos, Suzuki coupling.

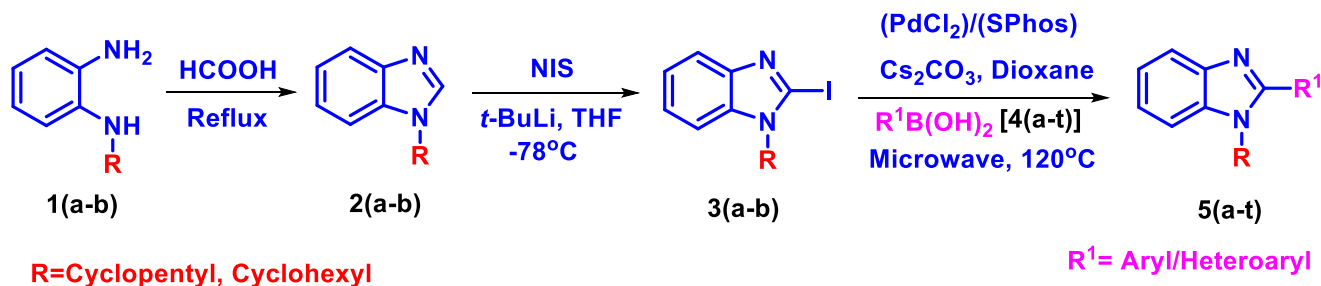
Introduction

Developing efficient synthetic protocols to access and functionalize an extensive range of structurally diverse aryl/heteroaryl scaffolds continues to play a significant role in the area of organic synthesis.¹ This late-stage diversification, which incorporates appendage diversity into the molecule, plays a vital role in optimizing the properties of potential drug candidates. Among the methodologies developed, palladium-mediated synthetic protocols play a major role in accessing and functionalizing a wide range of chemical frameworks. Among the various metal-mediated reactions, the Suzuki-Miyaura cross-coupling reaction continues to play a vital role as evidenced by its usage in many pharmaceutical and academic laboratories.²⁻⁷ The mild reaction condition makes Suzuki-Miyaura coupling different from other reactions which involve carbon-carbon bond formation.⁸ Moreover, this reaction also has other advantages, like high functional-group tolerance, and the commercial availability and stability of a wide variety of (hetero)aryl boronic acids.

Highly functionalized heterocyclic frameworks play a crucial role in medicinal chemistry, material science and agrochemical applications. Among heterocyclic systems, the benzimidazole core is found in many biologically relevant molecules which requires the functionalization of this framework using palladium-mediated cross-coupling reactions.⁹⁻¹⁶ As a part of our research efforts towards developing protocols that incorporate structural diversity into a heteroaromatic system,¹⁷⁻²⁶ we envisioned a Suzuki-Miyaura cross-coupling methodology to access 2-aryl/heteroaryl-substituted benzimidazoles. In recent years, the use of microwave energy in organic synthesis has gained much popularity in both industrial and academic research. By employing this efficient source of energy,²⁷⁻²⁹ compound libraries for lead-compound generation and optimization can be performed in a shorter period of time compared to classical thermal methods. By employing microwave-accelerated heating,³⁰⁻³² these reactions can be completed in very short times and with excellent yields of the products. The vast amount of literature depicting the vital role of microwave-assisted synthesis is well established.³³ Accordingly, our studies were focused on the use of microwave energy as an efficient energy source for the Suzuki-Miyaura coupling of benzimidazoles.

Results and Discussion

The methods of synthesis of benzimidazole include the condensation of 1,2-diaminobenzene with carboxylic acid, aldehydes or their derivatives in the presence of strong acids such as hydrochloric acid, polyphosphoric acid, p-toluene sulfonic acid, etc. Conversely, the low yields associated with these protocols, and the difficulty in isolation of pure products from crude reaction mixtures, increases the demand for more widely applicable synthetic methods to functionalize this vital scaffold. The above facts encouraged us to synthesize substituted benzimidazoles using a metal-mediated approach. In our new approach, we were interested in developing an efficient protocol for the syntheses of 1-(cyclohexyl/cyclopentyl)-2-disubstituted-benzimidazoles utilizing a microwave-promoted Suzuki-Miyaura reaction between substituted aryl/heteroaryl boronic acids and the common 1-(cyclohexyl/cyclopentyl)-2-iodobenzimidazole intermediates **3a** and **3b** (Scheme 1).



Scheme 1. Synthesis of iodo intermediates **3(a,b)** and Suzuki coupling with various boronic acids.

As depicted in Scheme 1, 2-iodo-1-substituted-benzimidazole is the key intermediate for the synthesis of the final target molecules **5(a-t)**. The compounds **2a** and **2b** were initially prepared by refluxing formic acid and cyclopentyl/cyclohexyl-substituted-1,2-diaminobenzene for 20 hours. The intermediate 2-iodo-1-substituted-benzimidazole compounds **3a** and **3b** were prepared in good yield by the reaction with *t*-butyllithium and N-iodosuccinamide in anhydrous THF. The obtained intermediates, **3a** and **3b**, were then treated with differently substituted aryl/heteroarylboronic acids **4(a-t)** using a Suzuki coupling reaction for synthesis of the targeted molecules. To optimize the final reaction conditions, a trial reaction was carried out with 1-cyclohexyl-2-iodo-1H-benzimidazole (**3a**) and 4-tolylboronic acid (**4b**) as the coupling partners. As a part of the initial screening, we tried different catalyst-ligand combinations, bases and solvents to get the best yield of the final Suzuki-coupled products (Table 1).

Table 1. Screening of different ligands for Suzuki coupling^a

Entry	Catalyst	Yield 5b (%) ^b
1	PdCl ₂ /BINAP	21 ^c
2	PdCl ₂ /DPPF	37
3	PdCl ₂ /DPPP	30
4	PdCl ₂ /SPhos	60
5	PdCl ₂ /Xantphos	31
6	PdCl ₂ /A-taphos	45

^aReaction conditions: **3a** (1 mmol), **4b** (1.6 mmol), PdCl₂ (5 mol%), Ligand (10 mol%), K₂CO₃ (2 mmol), DMF, microwave heating at 120 °C for 30 minutes.

^bGC-MS yield.

^cIsolated yield.

Initially, we carried out the reaction with a palladium chloride catalyst and 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP) ligand in DMF using K₂CO₃ as base. The reaction mixture was heated at 120 °C using a microwave synthesizer to obtain the desired product at 21 % final yield following purification using a flash-column chromatographic technique (Table 1, entry 1). Under this condition, we further screened different ligands to identify the suitable catalytic system which may simplify the conversion of the reactant molecules to the desired product in good yield (Figure 1). To our delight, we obtained the expected product **5b** in 60 % yield when 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (SPhos) was used as the ligand (Table 1, entry 4).

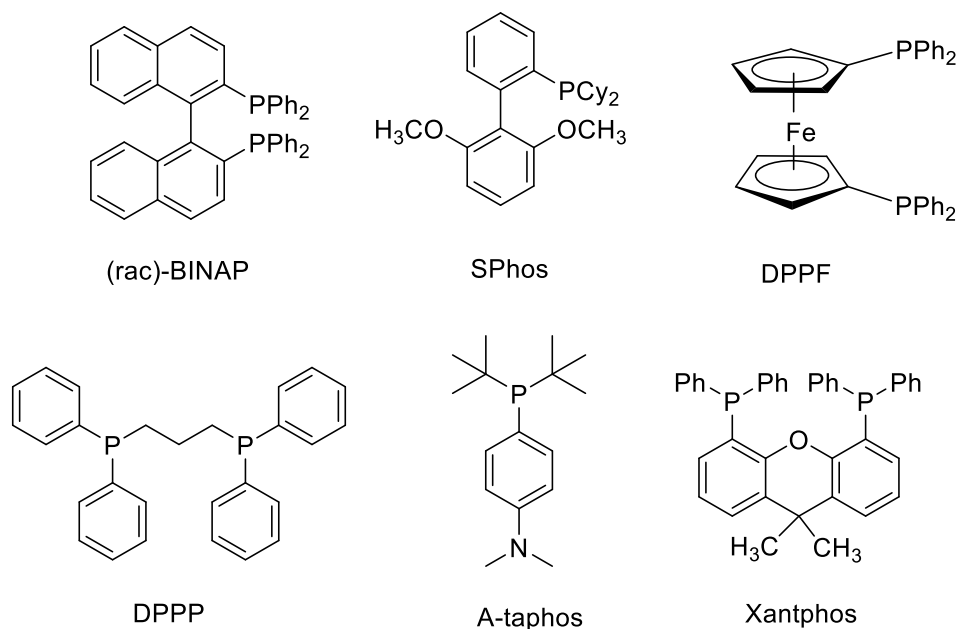


Figure 1. Different ligands used for screening for Suzuki coupling.

Our attention was next turned to screening various bases in view of improving the yield of the desired product. Accordingly, we screened various organic and inorganic bases using our previous best condition (Table 2). Comparing all of the bases used for the synthesis, cesium carbonate was found to be superior and more effective towards the catalytic system (Table 2, entry 4). Cesium salts are very versatile in their use in organic chemistry due to their large ionic radius, low charge density and, in many of the cases, superiority to the analogous potassium compounds. The reason for its unique success is not entirely clear, however, practice has proven its applicability. Organic bases and the non-nucleophilic base 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) were also used for our optimization investigation (Table 2: entries 1, 3 and 6). Unfortunately, the desired product was obtained in lower yields in all of those screening conditions.

Table 2. Screening of different bases for Suzuki coupling^a

Entry	Base	Yield 5b (%) ^b
1	DABCO	32
2	K ₂ CO ₃	60
3	TEA	20
4	Cs ₂ CO ₃	80
5	K ₃ PO ₄	40
6	DBU	30
7	KOH	5

^aReaction conditions: **3a** (1 mmol), **4a** (1.6 mmol), PdCl₂ (5 mol%), SPhos (10 mol%), Base (2 mmol), DMF, microwave heating at 120 °C for 30 minutes.

^bGC-MS yield.

We next focused on identifying the suitable solvent system which favors the reaction conditions (Table 3). To our delight, we found the formation of the expected product in 95 % (GC-MS yield) with 91 % isolated yield when dioxane was used as the solvent (Table 3, entry 6). Finally, the optimized conditions were fixed as microwave irradiation of the iodobenzimidazole intermediate **3a** and boronic acid in the PdCl₂-SPhos catalytic system with cesium carbonate as base and dioxane as solvent at 120 °C.

Table 3. Screening of different solvents for Suzuki coupling^a

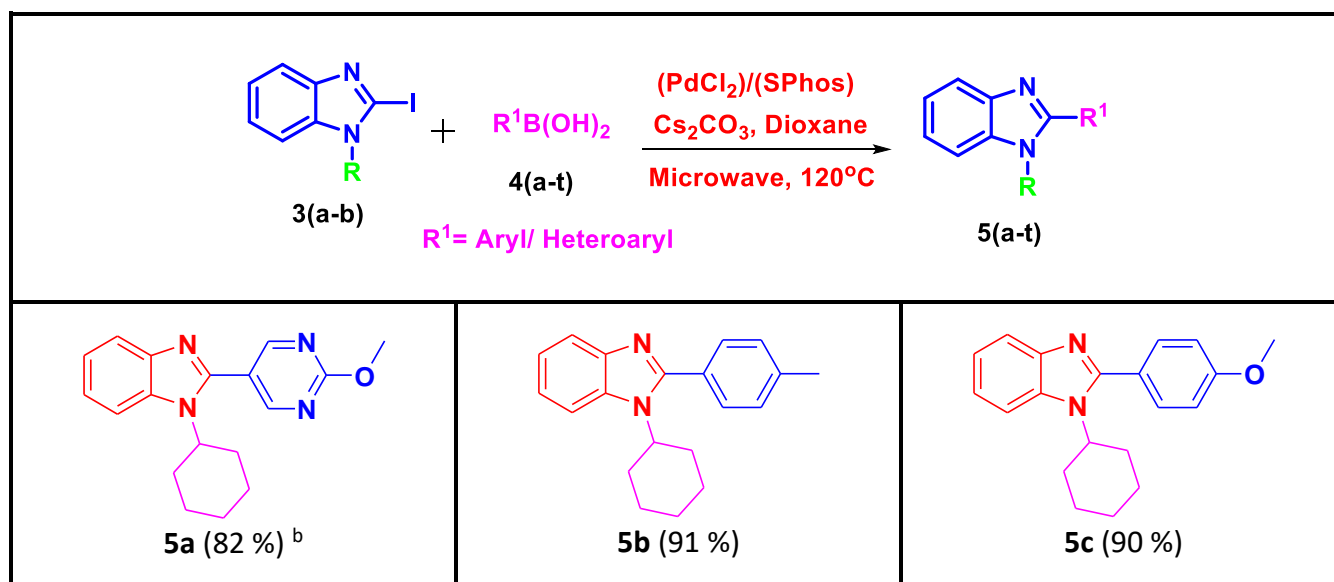
Entry	Solvent	Yield 5b (%) ^b
1	Toluene	20
2	THF	40
3	DME	30
4	DCE	50
5	DMF	80
6	Dioxane	95

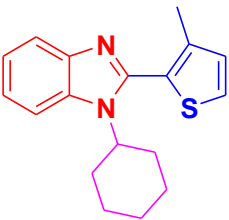
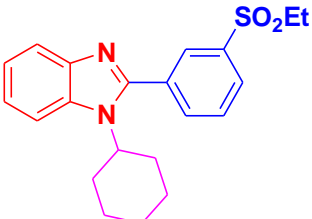
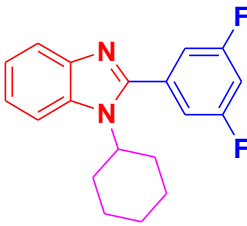
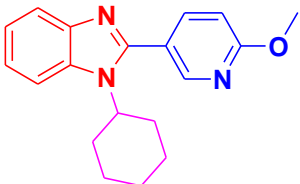
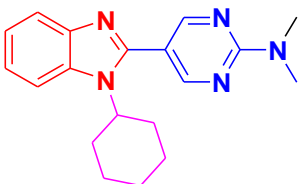
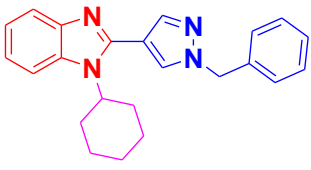
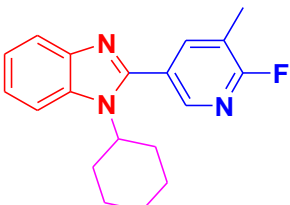
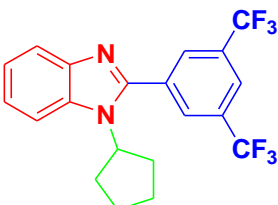
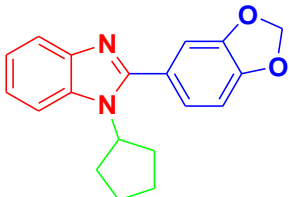
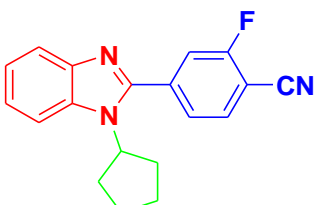
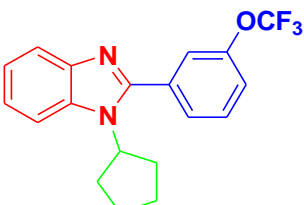
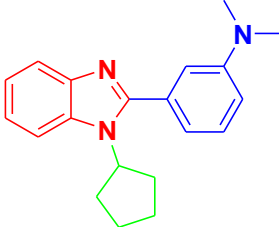
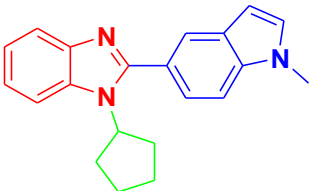
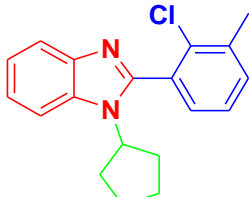
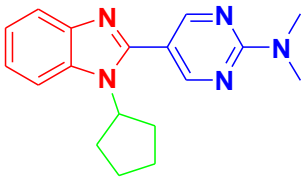
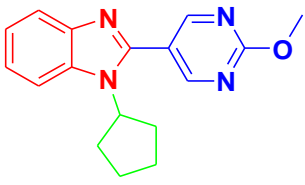
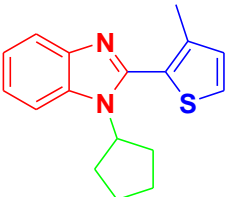
^aReaction conditions: **3a** (1 mmol), **4a** (1.6 mmol), PdCl₂ (5 mol%), SPhos (10 mol%), Cs₂CO₃ (2 mmol), solvent, microwave heating at 120 °C for 30 minutes.

^bGC-MS yield.

After establishing a facile protocol for the Suzuki coupling reaction, we focused our attention on the evaluation of the scope of this developed methodology. Accordingly, we treated the intermediates **3a** and **3b** with a variety of boronic acids in our optimized conditions under microwave irradiation. Almost all of the reactions were completed within 30-40 minutes. To our delight, we obtained the desired coupled products **5(a-t)** in good to excellent yields. The yield was consistent throughout the substrates irrespective of their electronic nature.

Table 4. Scope of Suzuki Coupling reactions with various boronic acids ^{a,b}



 <p>5d (84 %)</p>	 <p>5e (87 %)</p>	 <p>5f (90 %)</p>
 <p>5g (81 %)</p>	 <p>5h (90 %)</p>	 <p>5i (80 %)</p>
 <p>5j (86 %)</p>	 <p>5k (89 %)</p>	 <p>5l (86 %)</p>
 <p>5m (85 %)</p>	 <p>5n (90 %)</p>	 <p>5o (91 %)</p>
 <p>5p (88 %)</p>	 <p>5q (90 %)</p>	 <p>5r (86 %)</p>
 <p>5s (90 %)</p>	 <p>5t (85 %)</p>	

^aReaction conditions: 1-Cyclohexyl/cyclopentyl-2-iodo-benzimidazole (**3a**, **3b**) (1 mmol), boronic acid (1.6 mmol), PdCl₂ (5 mol%), SPhos (10 mol%), Cs₂CO₃ (2 mmol), dioxane, microwave irradiation at 120 °C for 30-40 minutes. ^bIsolated yield.

A plausible mechanism for the Suzuki-Miyaura cross-coupling reaction is as follows: the initially formed, coordinative-unsaturated palladium species $\text{LPd}(0)$ undergoes oxidative addition with the iodobenzimidazole intermediate to form the oxidative adduct complex. Subsequent *trans*-metalation from the ate-complex of boron to the oxidative adduct complex, followed by reductive elimination, yields the cross-coupled product.

Conclusions

A different approach for the synthesis of novel 1-substituted-2-(hetero)arylbenzimidazoles in excellent yields has been developed under microwave conditions. This method has provided easy access to a diverse range of 2-(hetero)arylbenzimidazoles of potential medicinal relevance. The protocol is found to be conducive with a wide range of electronically and sterically diverse (hetero)arylboronic acids. The use of a $\text{PdCl}_2/\text{SPhos}$ catalytic system was found to be influential in pushing these reactions to excellent conversions.

Experimental Section

General. All solvents and reagents were obtained from commercial suppliers and used without further purification unless otherwise noted. Microwave reactions were performed in a single mode Biotage Initiator Microwave Synthesizer, and temperature was monitored using infrared. Analytical TLC was performed on pre-coated aluminum sheets of silica (60 F 254 nm) and visualized by short-wave UV light at λ 254 nm. Melting points were determined on an EZ - Melt automated melting point apparatus. ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Bruker Avance II spectrometer with chemical shifts (δ) and coupling constants (J) expressed in ppm and Hz, respectively. The following abbreviations are used for the splitting patterns: s for singlet, d for doublet, t for triplet and m for multiplet. LC-MS analyses were performed using ESI/APCI, with an ATLANTIS C18 (50 X 4.6 mm-5 μm) column and a flow rate of 1.2 mL/min.

Synthesis of N-substituted derivatives 2a and 2b

N_1 -cyclohexylbenzene-1,2-diamine (10 mmol, 1.0 equiv), formic acid (10 equiv) and triethyl orthoformate (1.5 equiv) were refluxed at 100 $^\circ\text{C}$ for around 20 hours. Reaction completion was monitored by TLC. After completion of the reaction, the reaction mixture was distilled under reduced pressure yielding a black, oily crude mixture. The crude mixture was basified with saturated NaHCO_3 solution and the product was extracted using ethyl acetate (50 mL x 2). The combined organic layers were dried using anhydrous sodium sulphate, distilled under vacuum, and then purified by flash column chromatography using an eluent of 20-40 % ethyl acetate in hexane to give the intermediates **2a** and **2b**.

1-cyclohexyl-1H-benzimidazole (2a)

Brown oil (1800 mg, 90 %). ^1H NMR (400 MHz, CDCl_3): δ_{H} 1.27-1.29 (2H, m, CH_2 cyclohexyl), 1.30-1.34 (2H, m, CH_2 cyclohexyl), 1.91-1.94 (6H, m, 3CH_2 cyclohexyl), 4.53-4.56 (1H, m, NCH cyclohexyl), 7.23-7.25 (2H, m, 2CH aromatic), 8.04-8.07 (1H, m, CH aromatic), 8.33-8.35 (1H, m, CH aromatic), 8.54 (1H, s, CH aromatic). LC-MS: 201.3 (M+H). Anal. calcd for $\text{C}_{13}\text{H}_{16}\text{N}_2$ (200.28): C, 77.96; H, 8.05; N, 13.99. Found: C, 78.00; H, 8.09; N, 14.03.

1-cyclopentyl-1H-benzimidazole (2b)

Dark brown oil (1710 mg, 92 %). ^1H NMR (400 MHz, CDCl_3): δ_{H} 1.29-1.32 (2H, m, CH_2 cyclopentyl), 1.33-1.35 (2H, m, CH_2 cyclopentyl), 1.90-1.94 (4H, m, 2CH_2 cyclopentyl), 4.54-4.57 (1H, m, NCH cyclopentyl), 7.28-7.30 (2H, m, 2CH aromatic), 8.06-8.08 (1H, m, CH aromatic), 8.35-8.37 (1H, m, CH aromatic), 8.58 (1H, s, CH aromatic).

aromatic). LC-MS: 187.1 (M+H). Anal. calcd for $C_{12}H_{14}N_2$ (186.12): C, 77.38; H, 7.58; N, 15.04. Found: C, 77.50; H, 7.60; N, 15.09.

Synthesis of key intermediates 3a and 3b

In an oven dried flask, 1-cyclohexyl-*H*-benzimidazole (10 mmol, 1.0 equiv) was dissolved in dry THF. The reaction mixture was cooled to $-78\text{ }^{\circ}\text{C}$ and *t*-butyllithium (1.7 M, 1.4 equiv) was added dropwise at $-78\text{ }^{\circ}\text{C}$. The reaction mixture was stirred for 20 minutes and N-iodosuccinimide (NIS) (1.4 equiv) was added in anhydrous THF dropwise at $-78\text{ }^{\circ}\text{C}$ and stirred for 2 hours. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled to ambient temperature. The excess *t*-butyllithium was quenched using saturated NH_4Cl ; excess THF was distilled off and extracted twice with ethyl acetate (50 mL x 2). The combined organic layers were washed with brine, dried over anhydrous sodium sulphate, and distilled under reduced pressure to obtain the crude mixture. The crude product was then purified by flash-column chromatography using 10 % ethyl acetate to give the key iodobenzimidazole intermediates **3a** and **3b**.

1-cyclohexyl-2-iodo-1H-benzimidazole (3a)

Yellow powder (2900 mg, 89 %). mp $106\text{--}108\text{ }^{\circ}\text{C}$. ^1H NMR (400 MHz, CDCl_3): δ_{H} 1.45–1.48 (4H, m, 2CH_2 cyclohexyl), 1.89–1.92 (4H, m, 2CH_2 cyclohexyl), 2.64–2.68 (2H, m, CH_2 cyclohexyl), 4.41–4.44 (1H, m, NCH cyclohexyl), 7.22–7.25 (1H, m, CH aromatic), 7.98–8.01 (2H, m, 2CH aromatic), 8.27–8.30 (1H, m, CH aromatic). LC-MS: 327.2 (M+H). Anal. calcd for $C_{13}H_{15}\text{IN}_2$ (326.18): C, 47.87; H, 4.64; N, 8.59. Found: C, 47.94; H, 4.70; N, 8.63.

1-cyclopentyl-2-iodo-1H-benzimidazole (3b)

Yellow solid (2810 mg, 90 %). mp $103\text{--}105\text{ }^{\circ}\text{C}$. ^1H NMR (400 MHz, CDCl_3): δ_{H} 1.76–1.80 (2H, m, CH_2 cyclopentyl), 2.14–2.18 (4H, m, 2CH_2 cyclopentyl), 2.58–2.61 (2H, m, CH_2 cyclopentyl), 4.93–4.96 (1H, m, NCH cyclopentyl), 7.14–7.16 (1H, m, CH aromatic), 7.93–7.95 (2H, m, 2CH aromatic), 8.26–8.28 (1H, m, CH aromatic). LC-MS 313.2 (M+H). Anal. calcd for $C_{12}H_{13}\text{IN}_2$ (312.15): C, 46.17; H, 4.20; N, 8.97. Found: C, 46.23; H, 4.28; N, 9.04.

Synthesis of 2-substituted benzimidazole molecules 5(a-t)

To the key iodobenzimidazole intermediates **3(a-b)** (1 mmol, 1 equiv) in dioxane (4 mL) was added PdCl_2 (5 mol%) and SPhos (10 mol%), and the reaction mixture was degasified using nitrogen and stirred at ambient temperature for about 10 minutes. After 10 minutes, aryl/hetero aryl boronic acid **4(a-t)** (1.6 equiv) and CsCO_3 (2 equiv) were added and the reaction mixture was again degasified for another five minutes. The reaction mixture was heated in microwave at $120\text{ }^{\circ}\text{C}$ for 30–40 minutes. After the completion of reaction monitored by TLC, the reaction mixture was cooled to room temperature and 10 mL of water was added. The mixture was extracted using ethyl acetate and the organic layer was separated. The organic layer was dried using anhydrous sodium sulphate and distilled under reduced pressure to obtain the crude mixture. The crude product was purified by flash chromatography to afford the 2-substituted-benzimidazoles **5(a-t)** in good yields.

1-Cyclohexyl-2-(2-methoxypyrimidin-5-yl)benzimidazole (5a)

White solid (253 mg, 82 %). mp $132\text{--}138\text{ }^{\circ}\text{C}$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ_{H} 1.37–1.40 (2H, m, CH_2 cyclohexyl), 1.54–1.56 (4H, m, 2CH_2 cyclohexyl), 2.43–2.46 (4H, m, 2CH_2 cyclohexyl), 3.97–3.99 (1H, m, NCH cyclohexyl), 4.14 (3H, s, OCH_3), 7.14 (2H, d, J 6.8 Hz, 2CH aromatic), 7.93 (2H, d, J 6.8 Hz, 2CH aromatic), 8.61 (2H, s, 2CH aromatic). ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$): δ_{C} 21.7 ($\text{CH}_2 \times 2$ cyclohexyl), 27.4 (CH_2 cyclohexyl), 32.9 ($\text{CH}_2 \times 2$ cyclohexyl), 52.4 (OCH_3), 54.1 (NCH cyclohexyl), 106.9 (CH aromatic), 116.7 (CH aromatic), 119.3 (C aromatic), 121.9 (CH x 2 aromatic), 135.6 (C aromatic), 137.4 (C aromatic), 147.2 (CH x 2 aromatic), 154.7 (C aromatic), 166.4 (C aromatic). LC-MS (ESI-MS) m/z = 308.2 (M+1). Anal. calcd for $C_{18}H_{20}\text{N}_4\text{O}$ (308.16): C, 70.11; H, 6.54; N, 18.17. Found: C, 70.23; H, 6.61; N, 18.23.

1-Cyclohexyl-2-p-tolyl-benzoimidazole (5b)

Semisolid (264 mg, 91 %). ^1H NMR (400 MHz, DMSO- d_6): δ_{H} 1.30-1.34 (2H, m, CH_2 cyclohexyl), 1.48-1.52 (4H, m, 2CH_2 cyclohexyl), 2.34-2.37 (4H, m, 2CH_2 cyclohexyl), 2.57 (3H, s, CH_3), 3.71-3.74 (1H, m, NCH cyclohexyl), 6.99 (2H, d, J 7.2 Hz, 2CH aromatic), 7.27 (2H, d, J 7.2 Hz, 2CH aromatic), 7.30 (2H, d, J 6.4 Hz, 2CH aromatic), 7.96 (2H, d, J 7.6 Hz, 2CH aromatic). ^{13}C NMR (100 MHz, DMSO- d_6): δ_{C} 21.7 ($\text{CH}_2 \times 2$ cyclohexyl), 23.7 (CH_3), 27.4 (CH_2 cyclohexyl), 32.9 ($\text{CH}_2 \times 2$ cyclohexyl), 54.2 (NCH cyclohexyl), 116.8 (CH aromatic), 119.3 (CH aromatic), 122.0 (CH aromatic), 126.5 (CH aromatic), 128.9 (C aromatic), 131.5 (CH aromatic), 135.8 (CH aromatic), 137.5 (C aromatic), 139.5 (C aromatic), 147.3 (C aromatic), 154.8 (C aromatic). LC-MS (ESI-MS) m/z = 291.4 (M+1). Anal. calcd for $\text{C}_{20}\text{H}_{22}\text{N}_2$ (290.41): C, 82.72; H, 7.64; N, 9.65. Found: C, 82.83; H, 7.71; N, 9.68.

1-Cyclohexyl-2-(4-methoxyphenyl)-benzimidazole (5c)

Brown liquid (276 mg, 90 %). ^1H NMR (400 MHz, DMSO- d_6): δ_{H} 1.34-1.37 (2H, m, CH_2 cyclohexyl), 1.52-1.56 (4H, m, 2CH_2 cyclohexyl), 2.30-2.33 (4H, m, 2CH_2 cyclohexyl), 3.58 (3H, s, OCH_3), 3.60-3.63 (1H, m, NCH cyclohexyl), 6.87 (2H, d, J 6.4 Hz, 2CH aromatic), 7.20 (2H, d, J 6.4 Hz, 2CH aromatic), 7.42 (2H, d, J 7.2 Hz, 2CH aromatic), 7.82 (2H, d, J 7.2 Hz, 2CH aromatic). ^{13}C NMR (100 MHz, DMSO- d_6): δ_{C} 21.9 ($\text{CH}_2 \times 2$ cyclohexyl), 27.7 (CH_2 cyclohexyl), 32.9 ($\text{CH}_2 \times 2$ cyclohexyl), 52.9 (OCH_3), 54.8 (NCH cyclohexyl), 115.2 (CH aromatic), 117.4 (C aromatic), 119.3 (CH aromatic), 121.0 (CH aromatic), 124.6 (CH aromatic), 129.4 (CH aromatic), 135.1 (CH aromatic), 138.4 (C aromatic), 148.9 (C aromatic), 155.5 (C aromatic), 162.1 (C aromatic). LC-MS (ESI-MS) m/z = 307.4 (M+1). Anal. calcd for $\text{C}_{20}\text{H}_{22}\text{N}_2\text{O}$ (306.41): C, 78.40; H, 7.24; N, 9.14. Found: C, 78.53; H, 7.29; N, 9.17.

1-Cyclohexyl-2-(3-methylthiophen-2-yl)-benzimidazole (5d)

Off-white solid (249 mg, 84 %). mp 140-145 °C. ^1H NMR (400 MHz, DMSO- d_6): δ_{H} 1.26-1.29 (2H, m, CH_2 cyclohexyl), 1.62-1.65 (4H, m, 2CH_2 cyclohexyl), 2.28-2.32 (4H, m, 2CH_2 cyclohexyl), 3.17 (3H, s, CH_3), 3.74-3.77 (1H, m, NCH cyclohexyl), 5.64 (1H, d, J 6.0 Hz, CH aromatic), 6.68 (1H, d, J 6.4 Hz, CH aromatic), 7.20 (1H, d, J 7.2 Hz, CH aromatic), 7.26 (1H, d, J 6.8 Hz, CH aromatic), 7.74 (1H, d, J 7.2 Hz, CH aromatic), 7.82 (1H, d, J 6.8 Hz, CH aromatic). ^{13}C NMR (100 MHz, DMSO- d_6): δ_{C} 11.2 (CH_3), 21.8 ($\text{CH}_2 \times 2$ cyclohexyl), 27.3 (CH_2 cyclohexyl), 33.0 ($\text{CH}_2 \times 2$ cyclohexyl), 54.6 (NCH cyclohexyl), 116.2 (CH aromatic), 119.5 (CH aromatic), 122.0 (CH aromatic), 124.9 (CH aromatic), 127.1 (CH aromatic), 134.1 (CH aromatic), 135.4 (C aromatic), 137.5 (C aromatic), 139.2 (C aromatic), 142.9 (C aromatic), 144.1 (C aromatic). LC-MS (ESI-MS) m/z = 297.4 (M+1). Anal. calcd for $\text{C}_{18}\text{H}_{20}\text{N}_2\text{S}$ (296.43): C, 72.93; H, 6.80; N, 9.45. Found: C, 73.00; H, 6.87; N, 9.51.

1-Cyclohexyl-2-(3-(ethylsulfonyl)phenyl)-benzimidazole (5e)

Brown solid (321 mg, 87 %). mp 150-154 °C. ^1H NMR (400 MHz, DMSO- d_6): δ_{H} 1.19 (3H, t, CH_3), 1.29-1.32 (2H, m, CH_2 cyclohexyl), 1.62-1.66 (4H, m, 2CH_2 cyclohexyl), 2.51-2.54 (4H, m, 2CH_2 cyclohexyl), 3.88-3.90 (2H, m, CH_2), 3.96-3.99 (1H, m, NCH cyclohexyl), 7.17 (2H, d, J 7.6 Hz, 2CH aromatic), 7.43 (1H, d, J 7.6 Hz, CH aromatic), 7.69 (1H, t, CH aromatic), 7.93 (1H, d, J 7.2 Hz, CH aromatic), 7.98 (1H, d, J 7.2 Hz, CH aromatic), 8.14 (1H, s, CH aromatic), 8.37 (1H, s, CH aromatic). ^{13}C NMR (100 MHz, DMSO- d_6): δ_{C} 5.4 (CH_3), 21.5 ($\text{CH}_2 \times 2$ cyclohexyl), 27.7 (CH_2 cyclohexyl), 32.6 ($\text{CH}_2 \times 2$ cyclohexyl), 52.1 (CH_2), 54.7 (NCH cyclohexyl), 115.8 (CH aromatic), 119.9 (CH aromatic), 123.2 (CH aromatic), 124.7 (CH aromatic), 128.9 (CH aromatic), 131.4 (CH aromatic), 132.7 (CH aromatic), 134.0 (C aromatic), 135.3 (CH aromatic), 137.9 (C aromatic), 140.0 (C aromatic), 146.2 (C aromatic), 154.1 (C aromatic). LC-MS (ESI-MS) m/z = 369.5 (M+1). Anal. calcd for $\text{C}_{21}\text{H}_{24}\text{N}_2\text{O}_2\text{S}$ (368.49): C, 68.45; H, 6.56; N, 7.60. Found: C, 68.64; H, 6.64; N, 7.63.

1-Cyclohexyl-2-(3,5-difluorophenyl)-benzimidazole (5f)

Semisolid (281 mg, 90 %). mp 158-162 °C. ^1H NMR (400 MHz, DMSO- d_6): δ_{H} 1.41-1.44 (2H, m, CH_2 cyclohexyl), 1.50-1.54 (4H, m, 2CH_2 cyclohexyl), 2.47-2.49 (4H, m, 2CH_2 cyclohexyl), 3.80-3.83 (1H, m, NCH cyclohexyl), 6.82 (1H, s, CH aromatic), 7.19 (1H, d, J 6.8 Hz, CH aromatic), 7.21 (1H, d, J 6.8 Hz, CH aromatic), 7.29 (2H, s, 2CH aromatic), 7.93 (1H, d, J 7.2 Hz, CH aromatic), 7.98 (1H, d, J 7.2 Hz, CH aromatic). ^{13}C NMR (100 MHz, DMSO-

d_6): δ_C 22.0 (CH₂ x 2 cyclohexyl), 27.1 (CH₂ cyclohexyl), 32.8 (CH₂ x 2 cyclohexyl), 54.4 (NCH cyclohexyl), 104.1 (CH aromatic), 112.2 (CH aromatic), 116.2 (CH aromatic), 119.5 (CH aromatic), 121.7 (CH aromatic), 124.1 (CH aromatic), 135.6 (C aromatic), 137.5 (C aromatic), 147.5 (C aromatic), 154.1 (C aromatic), 166.0 (CF aromatic). LC-MS (ESI-MS) m/z = 313.4 (M+1). Anal. calcd for C₁₉H₁₈F₂N₂ (312.36): C, 73.06; H, 5.81; N, 8.97. Found: C, 73.19; H, 5.92; N, 9.01.

1-Cyclohexyl-2-(6-methoxyppyridin-3-yl)-benzimidazole (5g)

Yellow oil (249 mg, 81 %). ¹H NMR (400 MHz, DMSO- d_6): δ_H 1.38-1.40 (2H, m, CH₂ cyclohexyl), 1.54-1.57 (4H, m, 2CH₂ cyclohexyl), 2.43-2.47 (4H, m, 2CH₂ cyclohexyl), 3.96-3.99 (1H, m, NCH cyclohexyl), 4.14 (3H, s, OCH₃), 6.84 (1H, d, J 6.0 Hz, CH aromatic), 7.19 (2H, d, J 6.0 Hz, 2CH aromatic), 7.96 (2H, d, J 7.6 Hz, 2CH aromatic), 8.36 (2H, s, 2CH aromatic). ¹³C NMR (100 MHz, DMSO- d_6): δ_C 21.4 (CH₂ x 2 cyclohexyl), 27.0 (CH₂ cyclohexyl), 32.7 (CH₂ x 2 cyclohexyl), 54.1 (NCH cyclohexyl), 56.4 (OCH₃), 110.2 (CH aromatic), 116.4 (CH aromatic), 119.8 (CH aromatic), 120.8 (C aromatic), 122.1 (CH aromatic), 122.7 (CH aromatic), 134.5 (CH aromatic), 135.4 (C aromatic), 140.1 (C aromatic), 141.6 (CH aromatic), 154.2 (C aromatic), 162.4 (C aromatic). LC-MS (ESI-MS) m/z = 308.4 (M+1). Anal. calcd for C₁₉H₂₁N₃O (307.39): C, 74.24; H, 6.89; N, 13.67. Found: C, 74.32; H, 6.94; N, 13.71.

5-(1-Cyclohexyl-benzimidazol-2-yl)-N,N-dimethylpyrimidin-2-amine (5h)

White semisolid (289 mg, 90 %). ¹H NMR (400 MHz, DMSO- d_6): δ_H 1.31-1.34 (2H, m, CH₂ cyclohexyl), 1.48-1.52 (4H, m, 2CH₂ cyclohexyl), 2.35-2.38 (4H, m, 2CH₂ cyclohexyl), 2.51 (6H, s, 2NCH₃), 3.71-3.74 (1H, m, NCH cyclohexyl), 7.10 (2H, d, J 7.2 Hz, 2CH aromatic), 7.83 (2H, d, J 7.2 Hz, 2CH aromatic), 8.97 (2H, s, 2CH aromatic). ¹³C NMR (100 MHz, DMSO- d_6): δ_C 21.7 (CH₂ x 2 cyclohexyl), 27.4 (CH₂ cyclohexyl), 32.9 (CH₂ x 2 cyclohexyl), 52.4 (NCH₃ x 2), 54.2 (NCH cyclohexyl), 116.7 (CH aromatic), 119.3 (CH aromatic), 121.1 (C aromatic), 121.9 (CH aromatic), 135.7 (CH aromatic), 137.5 (C aromatic), 147.2 (C aromatic), 150.5 (CH aromatic), 154.7 (C aromatic), 162.4 (C aromatic). LC-MS (ESI-MS) m/z = 322.4 (M+1). Anal. calcd for C₁₉H₂₃N₅ (321.42): C, 71.00; H, 7.21; N, 21.79. Found: C, 71.13; H, 7.29; N, 21.84.

2-(1-Benzyl-1H-pyrazol-4-yl)-1-cyclohexyl-1H-benzo[d]imidazole (5i)

White solid (285 mg, 80 %). mp 158-160 °C. ¹H NMR (400 MHz, DMSO- d_6): δ_H 1.38-1.40 (2H, m, CH₂ cyclohexyl), 1.54-1.58 (4H, m, 2CH₂ cyclohexyl), 2.44-2.47 (4H, m, 2CH₂ cyclohexyl), 3.96-3.99 (1H, m, NCH cyclohexyl), 5.08 (2H, s, benzylic CH₂), 7.06-7.11 (5H, m, 5CH aromatic), 7.14 (2H, d, J 6.8 Hz, 2CH aromatic), 7.21 (1H, s, CH aromatic), 7.34 (1H, s, CH aromatic), 7.93 (2H, d, J 6.8 Hz, 2CH aromatic). ¹³C NMR (100 MHz, DMSO- d_6): δ_C 21.7 (CH₂ x 2 cyclohexyl), 27.4 (CH₂ cyclohexyl), 32.9 (CH₂ x 2 cyclohexyl), 52.4 (CH₂ benzylic), 54.1 (NCH cyclohexyl), 103.6 (C aromatic), 116.7 (CH aromatic), 119.3 (CH aromatic), 121.9 (CH aromatic), 126.1 (CH aromatic), 127.0 (CH aromatic), 128.1 (CH aromatic), 129.3 (CH aromatic), 130.6 (CH aromatic), 135.1 (C aromatic), 135.4 (CH aromatic), 137.2 (C aromatic), 144.7 (C aromatic), 155.4 (C aromatic). LC-MS (ESI-MS) m/z = 357.5 (M+1). Anal. calcd for C₂₃H₂₄N₄ (356.47): C, 77.50; H, 6.79; N, 15.72. Found: C, 77.59; H, 6.94; N, 15.79.

1-Cyclohexyl-2-(6-fluoro-5-methylpyridin-3-yl)-benzimidazole (5j)

Pale yellow solid (266 mg, 86 %). mp 170-172 °C. ¹H NMR (400 MHz, DMSO- d_6): δ_H 1.42-1.45 (2H, m, CH₂ cyclohexyl), 1.47-1.51 (4H, m, 2CH₂ cyclohexyl), 2.30-2.34 (4H, m, 2CH₂ cyclohexyl), 2.81 (3H, s, CH₃), 3.79-3.82 (1H, m, NCH cyclohexyl), 7.04 (1H, d, J 6.4 Hz, CH aromatic), 7.32 (1H, d, J 6.4 Hz, CH aromatic), 7.84 (2H, d, J 8.0 Hz, 2CH aromatic), 8.47 (1H, s, CH aromatic), 8.87 (1H, s, CH aromatic). ¹³C NMR (100 MHz, DMSO- d_6): δ_C 14.2 (CH₃), 21.6 (CH₂ x 2 cyclohexyl), 27.4 (CH₂ cyclohexyl), 32.8 (CH₂ x 2 cyclohexyl), 54.2 (NCH cyclohexyl), 116.5 (CH aromatic), 119.3 (CH aromatic), 120.1 (C aromatic), 122.4 (CH aromatic), 129.8 (CH aromatic), 135.9 (CH aromatic), 136.8 (C aromatic), 139.9 (C aromatic), 140.2 (CH aromatic), 147.2 (C aromatic), 154.5 (C aromatic), 166.4 (CF aromatic). LC-MS (ESI-MS) m/z = 310.4 (M+1). Anal. calcd for C₁₉H₂₀FN₃ (309.38): C, 73.76; H, 6.52; N, 13.58. Found: C, 73.84; H, 6.63; N, 13.64.

2-(3,5-Bis(trifluoromethyl)phenyl)-1-cyclopentyl-1H-benzo[d]imidazole (5k)

White solid (355 mg, 89 %). mp 183-185 °C. ^1H NMR (400 MHz, DMSO- d_6): δ_{H} 1.39-1.42 (2H, m, CH_2 cyclopentyl), 1.57-1.60 (2H, m, CH_2 cyclopentyl), 2.60-2.64 (4H, m, 2CH_2 cyclopentyl), 3.69-3.73 (1H, m, NCH cyclopentyl), 6.99 (1H, s, CH aromatic) 7.29 (1H, d, J 6.8 Hz, CH aromatic), 7.31 (1H, d, J 6.8 Hz, CH aromatic), 7.39 (2H, s, 2CH aromatic), 7.84 (1H, d, J 7.6 Hz, CH aromatic), 7.90 (1H, d, J 7.6 Hz, CH aromatic). ^{13}C NMR (100 MHz, DMSO- d_6): δ_{C} 20.9 ($\text{CH}_2 \times 2$ cyclopentyl), 33.4 ($\text{CH}_2 \times 2$ cyclopentyl), 52.8 (NCH cyclopentyl), 115.9 (CH aromatic), 121.1 (CH aromatic), 124.5 (CH aromatic), 126.9 (CH aromatic), 127.2 (CH aromatic), 128.9 (C aromatic), 130.6 (C aromatic), 132.2 (CF_3 aromatic), 133.0 (C aromatic), 134.9 (C aromatic), 143.1 (C aromatic), 155.1 (C aromatic). LC-MS (ESI-MS) m/z = 399.4 (M+1). Anal. calcd for $\text{C}_{20}\text{H}_{16}\text{F}_6\text{N}_2$ (398.35): C, 60.30; H, 4.05; N, 7.03. Found: C, 60.39; H, 4.11; N, 7.07.

2-(Benzo[d][1,3]dioxol-5-yl)-1-cyclopentyl-1H-benzo[d]imidazole (5l)

Colorless liquid (263 mg, 86 %). ^1H NMR (400 MHz, DMSO- d_6): δ_{H} 1.59-1.61 (2H, m, CH_2 cyclopentyl), 1.98-2.01 (4H, m, 2CH_2 cyclopentyl), 2.83-2.85 (2H, m, CH_2 cyclopentyl), 3.33-3.35 (1H, m, NCH cyclopentyl), 6.14 (2H, s, OCH_2), 6.99 (1H, d, J 6.4 Hz, CH aromatic), 7.22-7.26 (3H, m, 3CH aromatic), 7.64 (2H, d, J 7.2 Hz, 2CH aromatic), 8.16-8.19 (1H, m, CH aromatic). ^{13}C NMR (100 MHz, DMSO- d_6): δ_{C} 20.1 ($\text{CH}_2 \times 2$ cyclopentyl), 33.6 ($\text{CH}_2 \times 2$ cyclopentyl), 56.1 (NCH cyclopentyl), 100.6 (OCH_2), 112.5 (CH aromatic), 114.5 (CH aromatic), 117.1 (CH aromatic), 119.4 (CH aromatic), 121.1 (CH aromatic), 123.6 (CH aromatic), 124.6 (CH aromatic), 125.1 (C aromatic), 133.1 (C aromatic), 139.1 (C aromatic), 147.2 (C aromatic), 148.2 (C aromatic), 155.6 (C aromatic). LC-MS (ESI-MS) m/z = 307.4 (M+1). Anal. calcd for $\text{C}_{19}\text{H}_{18}\text{N}_2\text{O}_2$ (306.36): C, 74.49; H, 5.92; N, 9.14. Found: C, 74.56; H, 5.97; N, 9.16.

4-(1-Cyclopentyl-1H-benzo[d]imidazol-2-yl)-2-fluorobenzonitrile (5m)

Off-white solid (260 mg, 85 %). mp 189-191 °C. ^1H NMR (400 MHz, DMSO- d_6): δ_{H} 1.61-1.63 (2H, m, CH_2 cyclopentyl), 1.98-2.02 (4H, m, 2CH_2 cyclopentyl), 2.79-2.81 (2H, m, CH_2 cyclopentyl), 3.31-3.34 (1H, m, NCH cyclopentyl), 7.18-7.21 (1H, m, CH aromatic), 7.68 (1H, d, J 7.6 Hz, CH aromatic), 7.86-7.89 (2H, m, 2CH aromatic), 8.18 (2H, d, J 7.2 Hz, 2CH aromatic), 8.21-8.23 (1H, m, CH aromatic). ^{13}C NMR (100 MHz, DMSO- d_6): δ_{C} 23.8 ($\text{CH}_2 \times 2$ cyclopentyl), 34.1 ($\text{CH}_2 \times 2$ cyclopentyl), 56.1 (NCH cyclopentyl), 112.5 (CH aromatic), 115.9 (C aromatic), 116.1 (CH aromatic), 117.6 (CH aromatic), 122.3 (CN), 124.5 (CH aromatic), 132.5 (CH aromatic), 134.2 (CH aromatic), 135.5 (C aromatic), 136.2 (CH aromatic), 139.1 (C aromatic), 144.4 (C aromatic), 159.6 (CF aromatic), 164.4 (C aromatic). LC-MS (ESI-MS) m/z = 306.4 (M+1). Anal. calcd for $\text{C}_{19}\text{H}_{16}\text{FN}_3$ (305.35): C, 74.74; H, 5.28; N, 13.76. Found: C, 74.80; H, 5.30; N, 13.72.

1-Cyclopentyl-2-(3-(trifluoromethoxy)phenyl)-1H-benzo[d]imidazole (5n)

White solid (312 mg, 90 %). mp 183-185 °C. ^1H NMR (400 MHz, DMSO- d_6): δ_{H} 1.62-1.65 (2H, m, CH_2 cyclopentyl), 2.02-2.06 (4H, m, 2CH_2 cyclopentyl), 2.70-2.73 (2H, m, CH_2 cyclopentyl), 4.00-4.03 (1H, m, NCH cyclopentyl), 7.19-7.22 (1H, m, CH aromatic), 7.33-7.36 (1H, m, CH aromatic), 7.59-7.62 (2H, m, 2CH aromatic), 8.10 (2H, d, J 7.2 Hz, 2CH aromatic), 8.28 (2H, d, J 7.2 Hz, 2CH aromatic). ^{13}C NMR (100 MHz, DMSO- d_6): δ_{C} 23.2 ($\text{CH}_2 \times 2$ cyclopentyl), 35.1 ($\text{CH}_2 \times 2$ cyclopentyl), 56.2 (NCH cyclopentyl), 110.8 (CH aromatic), 113.6 (CH aromatic), 117.1 (CH aromatic), 119.5 (CH aromatic), 121.2 (CH aromatic), 122.6 (CH aromatic), 129.6 (CH aromatic), 130.1 (C aromatic), 132.6 (OCF_3 aromatic), 134.2 (C aromatic), 137.1 (C aromatic), 142.9 (C aromatic), 155.1 (C aromatic), 160.2 (C aromatic). LC-MS (ESI-MS) m/z = 347.4 (M+1). Anal. calcd for $\text{C}_{19}\text{H}_{17}\text{F}_3\text{N}_2\text{O}$ (346.35): C, 65.89; H, 4.95; N, 8.09. Found: C, 65.94; H, 4.89; N, 12.13.

3-(1-Cyclopentyl-1H-benzo[d]imidazol-2-yl)-N,N-dimethylbenzenamine (5o)

Brown solid (278 mg, 91 %). mp 173-175 °C. ^1H NMR (400 MHz, DMSO- d_6): δ_{H} 1.60-1.63 (2H, m, CH_2 cyclopentyl), 1.97-2.01 (4H, m, 2CH_2 cyclopentyl), 2.68-2.70 (2H, m, CH_2 cyclopentyl), 3.11 (6H, s, 2NCH_3), 4.86-4.89 (1H, m, NCH cyclopentyl), 6.88-6.91 (1H, m, CH aromatic), 6.98 (1H, d, J 6.8 Hz, CH aromatic), 7.12 (1H, s,

CH aromatic), 7.30-7.33 (1H, m, CH aromatic), 7.38 (1H, t, CH aromatic), 8.09 (2H, d, *J* 6.8 Hz, 2CH aromatic), 8.24-8.26 (1H, m, CH aromatic). ¹³C NMR (100 MHz, DMSO-*d*₆): δ_c 23.2 (CH₂ x 2 cyclopentyl), 33.9 (CH₂ x 2 cyclopentyl), 42.4 (NCH₃), 53.8 (NCH cyclopentyl), 111.7 (CH aromatic), 115.8 (CH aromatic), 116.1 (CH aromatic), 117.7 (CH aromatic), 119.6 (CH aromatic), 123.3 (CH aromatic), 124.2 (CH aromatic), 132.7 (C aromatic), 133.4 (CH aromatic), 135.2 (C aromatic), 143.1 (C aromatic), 153.3 (C aromatic), 156.1 (C aromatic). LC-MS (ESI-MS) *m/z* = 306.4 (M+1). Anal. calcd for C₂₀H₂₃N₃ (305.42): C, 78.65; H, 7.59; N, 13.76. Found: C, 78.69; H, 7.62; N, 13.74.

1-Cyclopentyl-2-(1-methyl-1H-indol-5-yl)-1H-benzo[d]imidazole (5p)

Dark brown oil (278 mg, 88 %). ¹H NMR (400 MHz, DMSO-*d*₆): δ_H 1.65-1.68 (2H, m, CH₂ cyclopentyl), 2.00-2.04 (4H, m, 2CH₂ cyclopentyl), 2.08-2.10 (2H, m, CH₂ cyclopentyl), 3.67 (3H, s, NCH₃), 4.92-4.95 (1H, m, NCH cyclopentyl), 6.68 (1H, d, *J* 6.0 Hz, CH aromatic), 7.16 (1H, d, *J* 6.0 Hz, CH aromatic), 7.28-7.30 (1H, m, CH aromatic), 7.47 (1H, d, *J* 7.2 Hz, CH aromatic), 7.63-7.65 (1H, m, CH aromatic), 7.97 (1H, s, CH aromatic), 8.10-8.14 (2H, m, 2CH aromatic), 8.20 (1H, d, *J* 7.2 Hz, CH aromatic). ¹³C NMR (100 MHz, DMSO-*d*₆): δ_c 21.1 (CH₂ x 2 cyclopentyl), 34.2 (CH₂ x 2 cyclopentyl), 40.2 (NCH₃), 53.7 (NCH cyclopentyl), 106.2 (CH aromatic), 112.7 (CH aromatic), 115.3 (CH aromatic), 117.1 (CH aromatic), 120.0 (CH aromatic), 121.1 (CH aromatic), 123.6 (CH aromatic), 123.8 (CH aromatic), 129.6 (C aromatic), 130.1 (CH aromatic), 130.3 (C aromatic), 133.1 (C aromatic), 136.5 (C aromatic), 143.2 (C aromatic), 154.2 (C aromatic). LC-MS (ESI-MS) *m/z* = 316.4 (M+1). Anal. calcd for C₂₁H₂₁N₃ (315.42): C, 79.97; H, 6.71; N, 13.32. Found: C, 80.08; H, 6.79; N, 13.37.

2-(2-Chloro-3-methylphenyl)-1-cyclopentyl-1H-benzo[d]imidazole (5q)

Pale yellow solid (280 mg, 90 %). mp 193-195 °C. ¹H NMR (400 MHz, DMSO-*d*₆): δ_H 1.63-1.65 (2H, m, CH₂ cyclopentyl), 1.92-1.96 (4H, m, 2CH₂ cyclopentyl), 2.39 (3H, s, CH₃), 2.56-2.58 (2H, m, CH₂ cyclopentyl), 4.43-4.46 (1H, m, NCH cyclopentyl), 7.01-7.05 (3H, m, 3CH aromatic), 7.14 (1H, t, CH aromatic), 7.48 (2H, d, *J* 6.8 Hz, 2CH aromatic), 8.00 (1H, d, *J* 6.8 Hz, CH aromatic). ¹³C NMR (100 MHz, DMSO-*d*₆): δ_c 16.9 (CH₃), 23.6 (CH₂ x 2 cyclopentyl), 33.5 (CH₂ x 2 cyclopentyl), 53.7 (NCH cyclopentyl), 112.4 (CH aromatic), 118.1 (CH aromatic), 120.8 (CH aromatic), 121.3 (CH aromatic), 124.6 (CH aromatic), 128.0 (CH aromatic), 131.2 (CH aromatic), 132.6 (C aromatic), 134.1 (C aromatic), 136.1 (C aromatic), 137.2 (C aromatic), 141.3 (C aromatic), 155.1 (C aromatic). LC-MS (ESI-MS) *m/z* = 311.8 (M+1). Anal. calcd for C₁₉H₁₉ClN₂ (310.82): C, 73.42; H, 6.16; Cl, N, 9.01. Found: C, 73.48; H, 6.17; N, 9.00.

5-(1-Cyclopentyl-1H-benzo[d]imidazol-2-yl)-N,N-dimethylpyrimidin-2-amine (5r)

Colorless liquid (264 mg, 86 %). ¹H NMR (400 MHz, DMSO-*d*₆): δ_H 1.59-1.62 (2H, m, CH₂ cyclopentyl), 1.98-2.02 (4H, m, 2CH₂ cyclopentyl), 2.07-2.09 (2H, m, CH₂ cyclopentyl), 2.51 (6H, s, 2NCH₃), 4.43-4.46 (1H, m, NCH cyclopentyl), 7.11-7.15 (3H, m, 3CH aromatic), 7.21 (1H, t, CH aromatic), 8.00 (2H, s, 2CH aromatic). ¹³C NMR (100 MHz, DMSO-*d*₆): δ_c 22.2 (CH₂ x 2 cyclopentyl), 33.4 (CH₂ x 2 cyclopentyl), 42.6 (NCH₃), 53.4 (NCH cyclopentyl), 111.3 (CH aromatic), 117.8 (CH aromatic), 121.1 (CH aromatic), 122.1 (C aromatic), 123.8 (CH aromatic), 135.1 (C aromatic), 142.3 (C aromatic), 148.7 (CH aromatic), 155.1 (C aromatic), 163.3 (C aromatic). LC-MS (ESI-MS) *m/z* = 308.4 (M+1). Anal. calcd for C₁₈H₂₁N₅ (307.40): C, 70.33; H, 6.89; N, 22.78. Found: C, 70.38; H, 6.91; N, 22.84.

1-Cyclopentyl-2-(2-methoxypyrimidin-5-yl)-1H-benzo[d]imidazole (5s)

White solid (265 mg, 90 %). mp 188-190 °C. ¹H NMR (400 MHz, DMSO-*d*₆): δ_H 1.38-1.40 (2H, m, CH₂ cyclopentyl), 1.54-1.58 (4H, m, 2CH₂ cyclopentyl), 2.23-2.26 (2H, m, CH₂ cyclopentyl), 3.92-3.95 (1H, m, NCH cyclopentyl), 3.98 (3H, s, OCH₃), 7.14 (1H, d, *J* 6.4 Hz, CH aromatic), 7.18 (1H, d, *J* 6.4 Hz, CH aromatic), 7.93 (1H, d, *J* 7.6 Hz, CH aromatic), 7.98 (1H, d, *J* 7.6 Hz, CH aromatic), 8.61 (2H, s, 2CH aromatic). ¹³C NMR (100 MHz, DMSO-*d*₆): δ_c 22.2 (CH₂ x 2 cyclopentyl), 33.1 (CH₂ x 2 cyclopentyl), 53.1 (NCH cyclopentyl), 57.1 (OCH₃), 116.1 (CH aromatic), 119.4 (C aromatic), 120.0 (CH aromatic), 123.5 (CH aromatic), 124.2 (CH aromatic), 134.7

(C aromatic), 140.1 (C aromatic), 147.6 (CH aromatic), 156.2 (C aromatic), 164.1 (C aromatic). LC-MS (ESI-MS) m/z = 295.4 (M+1). Anal. calcd for $C_{17}H_{18}N_4O$ (294.35): C, 69.37; H, 6.16; N, 19.03. Found: C, 69.45; H, 6.19; N, 19.09.

1-Cyclopentyl-2-(3-methylthiophen-2-yl)-1H-benzo[d]imidazole (5t)

White crystalline solid (240 mg, 85 %). mp 169–171 °C. 1H NMR (400 MHz, DMSO- d_6): δ_H 1.36–1.39 (2H, m, CH_2 cyclopentyl), 1.58–1.60 (4H, m, $2CH_2$ cyclopentyl), 2.17–2.19 (2H, m, CH_2 cyclopentyl), 3.31 (3H, s, CH_3), 3.69–3.72 (1H, m, NCH cyclopentyl), 5.62 (1H, d, J 5.6 Hz, CH aromatic), 6.61 (1H, t, CH aromatic), 6.89 (1H, t, CH aromatic), 7.21 (1H, d, J 6.8 Hz, CH aromatic), 7.60 (1H, d, J 7.2 Hz, CH aromatic), 7.72 (1H, d, J 7.2 Hz, CH aromatic). ^{13}C NMR (100 MHz, DMSO- d_6): δ_C 13.6 (CH_3), 22.2 ($CH_2 \times 2$ cyclopentyl), 33.6 ($CH_2 \times 2$ cyclopentyl), 54.1 (NCH cyclopentyl), 111.5 (CH aromatic), 118.2 (CH aromatic), 123.1 (CH aromatic), 123.8 (CH aromatic), 126.6 (CH aromatic), 127.4 (CH aromatic), 134.2 (C aromatic), 135.6 (C aromatic), 138.7 (C aromatic), 140.2 (C aromatic), 142.4 (C aromatic). LC-MS (ESI-MS) m/z = 283.4 (M+1). Anal. calcd for $C_{17}H_{18}N_2S$ (282.40): C, 72.30; H, 6.42; N, 9.92. Found: C, 72.36; H, 6.48; N, 9.96.

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References

- David, C. B.; Luis, C.; Ian, C.; David, C. R.; Andrew, W. T.; David, M. W.; Anthony, W. *Nature Chemistry* **2018**, *10*, 383–394.
- Spencer, D. D.; Siang, E. L.; Deidre, L. S.; Gary, A. M. *J. Org. Chem.* **2009**, *74* (10), 3626–3631
<https://doi.org/10.1021/jo900152n>
- Giulia, M. M.; Sai, V.C.V.; Jesús, A. L. U.; Paola, B.; Steven, P. N.; Heiko, J.; Luigi, C.; Miquel, S.; Albert, P. *Organometallics* **2017**, *36* (11), 2088–2095.
- Jiajing, T.; Yonggang, C.; Hongmei, L.; Nobuyoshi, Y. *J. Org. Chem.* **2014**, *79* (18), 8871–8876.
<https://doi.org/10.1021/jo501326r>
- Sambasivarao, K.; Kakali, L.; Dhurke, K. *Tetrahedron* **2002**, *58*, 9633–9695.
[https://doi.org/10.1016/S0040-4020\(02\)01188-2](https://doi.org/10.1016/S0040-4020(02)01188-2)
- Kucukbay, H.; Sireci, N.; Yilmaz, U.; Akkurt, M.; Yalcin, S. P.; Tahir, M. N.; Ott, H. *Appl. Organometal. Chem.* **2011**, *25*, 255–261.
<https://doi.org/10.1002/aoc.1751>
- Kucukbay, H. *J.O.T.S.C.A.* **2017**, *4*, 1–22.
- Martin, R.; Buchwald, S. L. *Acc. Chem. Res.* **2008**, *41*(11), 1461–1473.
<https://doi.org/10.1021/ar800036s>
- Khalafi-Nezhad, A.; Rad, M. N. S.; Mohbatkar, H.; Asrari, Z.; Hemmateenejad, B. *Bioorg. Med. Chem.* **2005**, *13*, 1931–1938.
<https://doi.org/10.1016/j.bmc.2005.01.014>
- Evans, B. E.; Rittle, K. E.; DiPardo, R. M.; Freidinger, R. M.; Whitter, W. L.; Lundell, G. F.; Veber, D. F.; Anderson, P. S. *J. Med. Chem.* **1998**, *31*, 2235–2246.

<https://doi.org/10.1021/jm00120a002>

11. Bell, C. A.; Dykstra, C. C.; Naiman, N. A.; Cory, M.; Fairley, T. A.; Tidwell, R. R. *Antimicrobial agents and Chemotherapy* **1993**, 37, 2668–2673.
<https://doi.org/10.1128/AAC.37.12.2668>
12. Richter, J. E. *Am. J. Gastroenterol.* **1997**, 92, 30–35.
13. Yilmaz, U.; Tekin, S.; Bugday, N.; Yavuz, K.; Kucukbay, H.; Sandal, S. *Inorganica Chimica Acta* **2019**, 495, 118977.
<https://doi.org/10.1016/j.ica.2019.118977>
14. Apohan, E.; Yilmaz, U.; Yilmaz, O.; Serindag, A.; Kucukbay, H.; Yesilada, O.; Baran, Y. *J. Organomet. Chem.* **2017**, 828, 52–58.
<https://doi.org/10.1016/j.jorganchem.2016.11.020>
15. Bugday, N.; Kucukbay, F. Z.; Apohan, E.; Kucukbay, H.; Serindag, A.; Yesilada, O. *Lett. Org. Chem.* **2017**, 14, 198–206.
<https://doi.org/10.2174/1570178614666170203093406>
16. Yilmaz, U.; Kucukbay, H.; Celikesir, S. T.; Akkurt, M.; Buyukgungor, O. *Turk. J. Chem.* **2013**, 37, 721–733.
<https://doi.org/10.3906/kim-1207-18>
17. Ranjith, P. K.; Haridas, K. R.; Sajith, A. M.; Muralidharan, A. *Tetrahedron Lett.* **2013**, 54, 5126–5129.
<https://doi.org/10.1016/j.tetlet.2013.07.073>
18. Sajith, A. M.; Muralidharan, A. *Tetrahedron Lett.* **2012**, 53 (39), 5206–5210.
<https://doi.org/10.1016/j.tetlet.2012.07.028>
19. Sajith, A. M.; Muralidharan, A. *Tetrahedron Lett.* **2012**, 53 (9), 1036–1041.
<https://doi.org/10.1016/j.tetlet.2011.12.051>
20. Jayan, T. J.; Sajith, A. M.; Revanna, C. N.; Sheena, S. *Adv. Synth. Cat.* **2017**, 359(3), 419–425.
<https://doi.org/10.1002/adsc.201600736>
21. Karuvalam, R. P.; Haridas, K. R.; Nayak, S. K.; Row, T. N. G.; Rajeesh, P.; Rishikesan, R.; Kumari, N. S. *Eur. J. Med. Chem.* **2012**, 49, 172–182.
<https://doi.org/10.1016/j.ejmech.2012.01.008>
22. Ranjith, P. K.; Rajeesh, P.; Haridas, K. R.; Susanta, N. K.; Row, T. N. G.; Rishikesan, R.; Kumari, N. S. *Bioorg. Med. Chem. Lett.* **2013**, 23 (18), 5228–5234.
<https://doi.org/10.1016/j.bmcl.2013.06.072>
23. Ranjith, P. K.; Rajeesh, P.; Haridas, K. R.; Rathnasamy, R.; Nalilu, K. S. *Med. Chem. Res.* **2013**, 22, 4437–4454.
<https://doi.org/10.1007/s00044-012-0451-x>
24. Ranjith, P. K.; Pakkath, R.; Haridas, K. R.; Kumari, S. N. *Eur. J. Med. Chem.* **2014**, 71, 354–365.
<https://doi.org/10.1016/j.ejmech.2013.11.002>
25. Savitha, B.; Reddy, E. K.; Kumar, C.S. A.; Karuvalam, R. P.; Padusha, M. S. A.; Bakulev, V. A.; Narasimhamurthy, K. H.; Sajith, A. M.; Joy, M. N. *Tetrahedron Lett.* **2019**, In press,
<https://doi.org/10.1016/j.tetlet.2019.151332>.
26. Joy, M.N.; Bakulev, V.A. *AIP Conference Proceedings* **2019**, 2063, 030015.
27. Bentiss, F.; Lagrene, M.; Barby, D. *Tetrahedron Lett.* **2000**, 41, 1539–1541.
[https://doi.org/10.1016/S0040-4039\(99\)02350-3](https://doi.org/10.1016/S0040-4039(99)02350-3)
28. Besson, T.; Guillard, J.; Rees, C.W. *Tetrahedron Lett.* **2000**, 41, 1027–1030.
[https://doi.org/10.1016/S0040-4039\(99\)02221-2](https://doi.org/10.1016/S0040-4039(99)02221-2)
29. Ranu, B. C.; Hajra, A.; Jana, U. C. *Tetrahedron Lett.* **2000**, 41, 5891–5894.

[https://doi.org/10.1016/S0040-4039\(00\)00929-1](https://doi.org/10.1016/S0040-4039(00)00929-1)

30. Shaabani, A. *J. Chem. Res.* **1998**, 672–673.

<https://doi.org/10.1039/a708858b>

31. Ungurenasu, C. *Synthesis* **1999**, 1729–1730.

<https://doi.org/10.1055/s-1999-3593>

32. Bogdal, D.; Lukasiewics, M. *Synlett* **2000**, 143–145.

<https://doi.org/10.1055/s-2000-6440>

33. Oussaid, A.; Loupy, A. *J. Chem. Res.* **1997**, 342–343.

<https://doi.org/10.1039/a704561a>